Thimerosal & Vaccines

1. **Why is thimerosal used as a preservative in vaccines?**

Thimerosal is used as a preservative in some multi-dose vials of vaccines to prevent contamination. Preservatives are not required for vaccines in single-dose vials. As a preservative, thimerosal is added at the end of the production process to the bulk or final container to prevent contamination after multi-dose vials are opened. Today, all routinely recommended licensed pediatric vaccines that are currently being manufactured for the U.S. market are free of thimerosal as a preservative. Thimerosal still may be used in the early stages of manufacturing of certain vaccines, but is removed through a purification process, with only trace, or insignificant, amounts remaining.

2. **If thimerosal was used in vaccines for many years, why is it of concern now?**

The Food and Drug Administration (FDA) Modernization Act of 1997 called for the FDA to review and assess the risk of *all* mercury containing food and drugs. As part of this effort, the FDA conducted a review of mercury content in vaccines.

3. **What recommendations did the Federal government make with respect to thimerosal in vaccines?**

A review conducted by the Food and Drug Administration (FDA) concluded that the use of thimerosal as a preservative in vaccines might result in the intake of mercury during the first 6 months of life that exceeds the Environmental Protection Agency (EPA), but not the FDA, the Agency for Toxic Substances and Disease Registry (ATSDR), or the World Health Organization (WHO) guidelines for *methyl*mercury intake (Ball et al., 2001). Thimerosal contains *ethyl*mercury. Methylmercury is a related compound and has been more thoroughly researched than ethyl mercury. Thus, federal safety standards are based on information we have about methyl mercury.

FDA's review found no evidence of harm caused by doses of thimerosal in vaccines, except for minor local reactions (Ball et al., 2001). Nevertheless, in July 1999 the Public Health Service agencies (PHS), the American Academy of Pediatrics (AAP), and vaccine manufacturers agreed that thimerosal levels in vaccines should be reduced or eliminated as a precautionary measure, and the Food and Drug Administration (FDA) committed to expediting the review of new vaccines that do not contain thimerosal.

4. **What progress has been made since July 1999 in removing thimerosal from vaccines routinely recommended for infants?**

Substantial progress has been made in the effort to reduce thimerosal exposure from vaccines. At this time, all routinely recommended licensed pediatric vaccines that are

currently being manufactured for the U.S. market, contain no thimerosal or contain only trace amounts of thimerosal. The vaccines with trace amount of thimerosal licensed to date contain less than 0.5 micrograms of mercury per dose, that is, a given dose of vaccine contains less than 1 part per million.

Events that contributed to accomplishing this goal include the licensure of a thimerosal free Hepatitis B Vaccine (Recombinant) manufactured by Merck and Company in August 1999. FDA licensed another hepatitis B vaccine with trace amounts of thimerosal, manufactured by GlaxoSmithKline in March 2000. A supplement for a new formulation of Aventis Pasteur's DTaP Vaccine with only a trace amount of thimerosal was approved in March 2001. Additionally, Wyeth-Lederle Vaccines and Pediatrics now only markets a single-dose, thimerosal-free formulation of its Haemophilus b (Hib) Conjugate Vaccine in the U.S. Thus, two hepatitis B vaccines are thimerosal free, four Hib vaccines are thimerosal free, and two DTaP vaccines are thimerosal free.

Prior to the recent initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury via routine childhood vaccinations during the first six months of life was 187.5 micrograms. With the newly formulated vaccines, the maximum cumulative exposure during the first six months of life will now be less than three micrograms of mercury; this represents a greater than 98 percent reduction in the amount of mercury a child would receive from vaccines in the first six months of life.

5. **I've heard that children may be getting toxic levels of mercury from vaccines. Is that true?**

No. There is no evidence of harm caused by the minute doses of thimerosal in vaccines, except for minor effects like swelling and redness at the injection site due to sensitivity to thimerosal.

Most importantly, since 1999, newly formulated thimerosal preservative-free vaccines have been licensed. With the newly formulated vaccines, the maximum cumulative exposure during the first six months of life will now be less than three micrograms of mercury. No children are receiving toxic levels of mercury from vaccines.

6. **What research is being conducted by the Federal Government regarding the safety of vaccines containing thimerosal?**

There is no evidence to suggest that thimerosal in vaccines causes any health problems in children and adults beyond local hypersensitivity reactions (like redness and swelling at the injection site). However, efforts to remove thimerosal from the U.S. vaccine supply have been accompanied by research investigations to better assess the potential health effects of exposure to thimerosal containing vaccines:

- The National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) funds thimerosal research that focuses on better understanding of what happens to thimerosal once it is introduced into the body

and how this compares to current knowledge of methyl mercury pathways. At the University of Rochester, NIAID sponsored researchers are performing an assessment of mercury levels in infants receiving routine immunizations. In addition, NIAID and the National Institutes of Environmental Health Sciences (NIEHS) are funding studies comparing the pharmacokinetics and tissue distribution of thimerosal, ethyl mercury, and methyl mercury in non-human primates. Pharamacokinetics is the study of how an agent is absorbed, distributed, metabolized (broken down), and excreted. For more information go to http://www.niaid.nih.gov/factsheets/thimerosal.htm

- The Food and Drug Administration (FDA) has been actively addressing the issue of thimerosal as a preservative in vaccines. For information on FDA activities related to thimerosal and vaccines go to http://www.fda.gov/cber/vacine/thimerosal.htm

- The CDC used large automated databases that link vaccination and International Classification of Disease codes (ICD-9) stored in the medical records in three managed care organizations (i.e., the Vaccine Safety Datalink project, or VSD) to screen for any possible associations between exposure to thimerosal-containing vaccines and a variety of neurologic, developmental, and renal outcomes. In phase I of this investigation, using the data from 2 of the managed care organizations, CDC and VSD researchers found statistically significant associations between thimerosal and several neurodevelopmental disorders, including language delays, speech delays, attention deficit hyperactivity disorder (ADHD), unspecified developmental delays, stammering, sleep disorders, emotional disorders, and tics. However, the associations were not consistent between the two VSD sites. Reviews of these preliminary observations by expert consultants, first at CDC and then from outside CDC, identified many important limitations and potential biases in the data set, including weak and inconsistent statistical associations, potential inaccuracies in the diagnostic codes, ad inadequate control for socio-economic factors. In phase II of the investigation, CDC investigators obtained and examined data from a third managed care organization. Analyses of these data using the same methods and having similar limitations as in the above study, did not confirm results for speech or language delay and attention deficit disorder. The number of events was too small to examine the association with tics and the category of unspecified developmental delays was not defined clearly enough to permit reanalysis. CDC is developing a research protocol for a follow-up to this study.

- The CDC's Center for Environmental Health and the National Center for Health Statistics are doing a study looking at all mercury exposures and working with the National Health and Nutrition Examination Survey (NHANES). NHANES 4 will collect samples of blood, hair and urine from all women of reproductive age and children under 5 in order to assess mercury levels in the body from all sources of mercury a person can be exposed to in the environment. Findings of a study conducted using NHANES 3 data to check blood and hair mercury levels suggest

that the mercury levels in young children and in women of childbearing age are generally below the level considered hazardous (MMWR;50, 140-143).

7. **Does thimerosal cause autism?**

There is no evidence that any vaccine or vaccine additive increases the risk of developing autism or any other behavior disorder. Nonetheless, given the level of concern among parents and others regarding vaccines and autism, the CDC is committed to investigating this issue to the fullest extent possible, using the best scientific methods available.

For more information on autism and vaccines go to
www.cdc.gov/nip/vacsafe/concerns/autism/default.htm

8. **Did the preliminary Vaccine Safety Datalink (VSD) study described above find that exposure to thimerosal within the first three months of life increases a child's risk of developing autism?**

No. A statistically significant relationship between autism and thimerosal was not found in either the preliminary study or the later, larger analysis. While a graph in the preliminary report does show an apparent elevation in risk for autism among children exposed to a certain level of thimerosal (> 62.5ug) by the third month of life, this risk was not statistically significant and was likely a chance fluctuation. In fact, later analyses of additional cases showed that a child's exposure to thimerosal, either by three months of life *or* by seven months of life, did not increase his or her risk for developing autism. There was no suggestion of an increased risk for autism even among those children who were exposed to the highest levels of thimerosal by seven months of age (i.e., those receiving 162.5 ug, 175 ug, or more than 175 ug thimerosal by 7 months of age). These preliminary negative results from the VSD project, however, cannot be considered definitive since the study was not specifically designed to evaluate a complex condition such as autism. CDC is planning a more thorough investigation of thimerosal exposure through infant vaccines and risk of autism.

Researchers must study as many people as possible in order to detect rare vaccine side effects and to reduce the chance fluctuations that often occur when studies are done with smaller groups of people. The Vaccine Safety Datalink (VSD) project is a partnership between CDC and several large health maintenance organizations (HMO's). Children who are born into the HMO's are added to the study on an ongoing basis. Information is continually accumulated on children in the study and each HMO compiles and sends this data to the CDC on a yearly basis. Therefore, a major difference between the preliminary study and the later analyses (presented to the Institute of Medicine's Immunization Safety Review Committee on July 16, 2001) is one of size and duration of follow-up. The preliminary study included over 75,000 children (67 with autism) who were followed up no further than December of 1997, whereas the study that was presented to the Institute of Medicine (IOM) included over 130,000 children (169 with autism) followed up until May of 1998. A transcript of this presentation can be found at
http://www.iom.edu/IOM/IOMHome.nsf/Pages/Thimerosal+Agenda

9. **Great Britain experienced a rapid rise in autism among children born in the 1980's and early 1990's. Could this be due to thimerosal in vaccines?**

It is unlikely that the rapid increase in autism cases in the UK was due to thimerosal. The only vaccine in the UK's childhood immunization program that contains thimerosal is DTP. All other vaccines (OPV, BCG, MMR, Hib, menC) added to the program since the 1950's are and have always been thimerosal free. In addition, if thimerosal in vaccines were causing autism, we would expect to see a simultaneous increase in both thimerosal exposure and autism cases. However, from the 1950's on, there was no increase in the amount of thimerosal UK children were receiving from vaccines, yet there was a jump in autism cases in the 1980's.

A significant change in the UK's program did occur in 1990 when they accelerated their immunization schedule so vaccines would be given earlier (changed from 3, 5, and 8 months to 2, 3 and 4 months). However, the rate of autism was rising long before this change occurred (see Fombonne, 2001).

10. **I understand some people are sensitive to mercury and must avoid it. Do they have problems with thimerosal-containing vaccines?**

Some individuals experience local skin reactions such as redness and swelling that may suggest a delayed-type of minor allergic reaction following injection with products containing thimerosal. Research suggests that most people who have a contact or skin allergy to thimerosal will not have the reaction when thimerosal is injected under the skin (Forstrom, 1980; Jacobs 1982). A prior history of a minor reaction to thimerosal in a vaccine is not considered a contraindication to further vaccination with thimerosal-containing vaccines. Severe anaphylactic (allergic) reaction to any vaccine is a contraindication to further vaccination with the vaccine.

11. **Do measles, mumps, and rubella (MMR) vaccines contain thimerosal?**

No, MMR vaccine does not and never did contain thimerosal. Varicella (chickenpox), inactivated polio (IPV), and pneumococcal conjugate vaccines have also never contained thimerosal.

12. **Why are chemicals and other substances added to vaccines?**

Many foods and medicines, including vaccines, have chemicals added to them to prevent the growth of germs, reduce spoilage, and prevent it from losing its potency over time.

Some additives are used in the production of vaccines. Vaccines may include suspending fluid (e.g., sterile water, saline, or fluids containing protein); preservatives and stabilizers (e.g., albumin, phenols, and glycine); and adjuvants, or enhancers, that help the vaccine improve its immunogenicity (ability to protect against disease).

For more information on additives, go to:
http://www.cdc.gov/nip/vacsafe/concerns/gen/additives.htm

13. **How can I find out what chemical additives are in specific vaccines?**

Ask your healthcare provider or pharmacist for a copy of the vaccine package insert. The package insert lists ingredients in the vaccine and discusses any known adverse reactions.

References

1. Ball L, Ball R, Pratt RD. An assessment of thimerosal in childhood vaccines. *Pediatrics*. 2001; 107:1147-1154.
2. Forstrom L, Hannulksela M, Kousa M, Lehmuskallio E. Merthiolate hypersensitivity and vaccination. *Contact Dermatitis*. 1980; 6:241-245.
3. Jacobs RL, Lowe RS, Lanier BQ. Adverse reactions to tetanus toxoid. *JAMA*. 1982; 247:40-41.
4. Joint statement concerning removal of thimerosal from vaccines. The American Academy of Family Physicians (AAFP), American Academy of Pediatrics (AAP), Advisory Committee on Immunization Practices (ACIP), and United States Public Health Service (USPHS). Approved June 22, 2000.
5. Magos L. (2000). Review on the toxicity of ethylmercury, including its presence as a preservative in biological and pharmaceutical products. *J. Appl. Toxicol*. 2001; 21:1-5.
6. Mahaffey KR. Methylmercury: A new look at the risks. *Public Health Reports*. 1999; 114:397-415.
7. Toxicological Profile for Mercury (Update). Agency for Toxic Substances and Disease Registry, Public Health Service, US Department of Health and Human Services. Atlanta, GA, 1999.
8. Verstraeten T. CDC draft 6/1/00 US. Assessment of neurologic and renal impairment associated with thimerosal-containing vaccines.